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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,077	09/07/2006	Geir Christensen	3657-1037	6193

466 7590 12/09/2010
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209 Madison Street
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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1633

NOTIFICATION DATE	DELIVERY MODE
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12/09/2010

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No. 10/585,077	Applicant(s) CHRISTENSEN ET AL.	
	Examiner Anne Marie S. Wehbe	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 55-57, 59-68, 70-72, 74-88, 90-94, 102-104 and 109-116 is/are pending in the application.
- 4a) Of the above claim(s) 70-72, 74-88, 90-94, 102-104 and 109 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 55-57, 59-68 and 110-116 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicant's amendment and response received on 8/13/10 has been entered. New claims 110-116 have been added. Claims 55-57, 59-68, 70-72, 74-88, 90-94, 102-104, and 109-116 are currently pending in the instant application. Of these, claims 70-72, 74-88, 90-94, 102-104, and 109 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/1/10. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 55-57, 59-68, and 110-116 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Rejections - 35 USC § 112

The rejection of claims 55-57, 59-68 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained and further applied to new claims 110-116. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The rejection of record identified the following scope of enablement: the specification, while being enabling for a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α -MHC promoter, and a

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transgenic mouse model of heart failure wherein said transgenic mouse model is made by administering tamoxifen to a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α -MHC promoter, wherein the administration of tamoxifen result in the Cre mediated deletion of exons 2 and 3 in both copies of the SERCA2 gene, and wherein the mouse develops heart failure by day 52 following tamoxifen administration, does not reasonably provide enablement for a transgenic mouse in which any genomic Serca ATPase gene has recombination sites inserted in both gene copies.

The applicant argues the since the Office acknowledges that the specification teaches a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer gene under transcriptional control of the alpha-MHC promoter that the specification enables everything within the scope of the claims. The applicant further argues that there is no requirement that all embodiments of a claimed invention be enabled and that while in their opinion the Office Action appears to require that the specification teach the reasons for lethality in Serca 1 negative and Serca2 negative mice, the claims as written do not encompass any mouse model of disease.

In response, it is well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991) (emphasis added by examiner). 35 U.S.C. § 112 also requires that the scope of the claims must

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bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). As stated in the previous office action, the specification broadly discloses the use of inserted heterologous recombination sites to induce targeted disruptions in Serca ATPase genes in transgenic mice to generate mouse models for various diseases, and in particular heart disease. The previous office action further analyzed the scope of the claimed invention, noting that while the claims as written encompass various mouse products which are disclosed in the specification as being useful for the production of a mouse model of Serca ATPase related diseases, the claimed mice, with the exception of new claims 111-112, do not actually encompass any mouse model of disease as none of the claimed embodiments of the transgenic mouse recite that the Serca ATPase gene has been disrupted. Thus, the claims under examination are drawn to intermediate mouse products with no reported phenotype whose sole use is identified in the specification as the production of a mouse model of Serca ATPase related disease. Note that new claims 111-112 do in fact recite that mouse with a null mutation in each genomic copy of the Serca2 gene, such that their use as a mouse model of disease is particularly relevant to enablement. Thus, a determination of whether the instant claims are enabled by the specification must include a determination of whether the scope of the claimed mice are enabled for use in the production of a mouse model of Serca ATPase related disease.

With this in mind, the previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation

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necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons for the finding of a lack of enablement for full scope of the invention as claimed. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702).

The previous office action pointed out that the specification fails to provide an enabling disclosure for making the breadth of transgenic mice encompassed by the claims, or for using the breadth of transgenic mice encompassed by the claims to produce a mouse model of any disease. In regards to making the breadth of mice encompassed by the claims, it was indeed acknowledged that the specification provides sufficient disclosure for making a transgenic mouse in which two or more loxP site have been inserted into a Serca ATPase gene (Serca1, Serca2, or Serca3). However, it was also noted that the specification fails to provide an enabling disclosure for making a transgenic mouse which further comprise a recombinase gene, such as Cre recombinase, that is expressed and active during embryonic and neonatal development. The prior art clearly teaches that the lack of Serca2 during embryogenesis in mice results in an embryonic lethal phenotype such that no Serca2 $-/-$ mice are produced (see Periasamy et al., of record). The prior art also teaches that the lack of Serca1 during embryonic development results in neonatal lethality just hours after birth (Pan et al. (2003) J. Biol. Chem., Vol. 278 (15), 13367-13375). Thus, the prior art clearly establishes that transgenic mice useful as a model of disease cannot be made where the genome of the mouse comprises two loxP or any other recombination sites in a Serca ATPase gene and which further comprises a heterologous nucleic acid encoding a Cre recombinase or any other recombinase where an active form of Cre recombinase is expressed

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during embryonic development. All these embodiments are encompassed by the broadest instant claims, see in particular dependent claims 61-68. Further, since neither the prior art nor the instant specification definitively teaches the reasons for early lethality in Serca1 negative and Serca2 negative mice, i.e. which organ(s) or tissue(s) affected by the lack of a Serca ATPase gene are the cause of death, the skilled artisan would not have been able to predict without undue experimentation whether tissue specific expression of the recombinase in any particular tissue, including heart, could avoid the lethal phenotype associated with a homozygous Serca ATPase deletion during embryonic development. Please note that contrary to applicant's comments, the office action did not require that the specification teach the reasons behind embryonic lethality in Serca knockout mice, the office action simply pointed out that the reasons for early lethality in Serca1 negative and Serca2 negative mice were not known at the time of filing, thus creating a high degree of unpredictability as to whether tissue specific expression of the recombinase in any particular tissue, including heart, could avoid the lethal phenotype.

Finally, it is not agreed that the disclosure of a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer gene under transcriptional control of the alpha-MHC promoter enables everything within the scope of the claims. The previous office action provided a detailed analysis as to why the breadth of the claims was not enabled by this embodiment. This analysis is reiterated below for applicant's convenience.

The previous office action discussed that the specification does not provide an enabling disclosure for making or using a transgenic mouse which comprises two or more recombination sites in any location of a Serca ATPase gene and which further comprises any inducible Cre

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recombinase or other recombinase gene. The claims as written read broadly on the placement of the recombination sites anywhere in the Serca ATPase gene such that deletion of the flanked sequence may or may not result in any effect on expression of a functional protein, i.e. the recombination sites could be located within an intron. While the working examples provide specific guidance for the insertion of loxP sites flanking exons 2 and 3 of the Serca2 gene such that recombination of the sites creates a null mutation, the claims are not so limited and encompass the generation of any deletion in the genomic gene sequence. The specification provides no guidance for the enormous number of potential mutations to the genomic gene, or the consequences of any of these mutations on expression of a protein or partial protein product from the mutated gene. The specification further fails to provide any guidance as to the activity or lack thereof of any partial Serca ATPase gene product. Thus, with the exception of the deletion of exons 2 and 3 of the Serca2 gene, the specification fails to provide the requisite guidance for the phenotype of the genus of transgenic mice produced by recombination of the inserted recombination sites as claimed. Note that “case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves.” *In re Gardner* 166 USPQ 138 (CCPA) 1970.

In regards to the generation of a null deletion in a Serca ATPase gene, the specification teaches that the embryonic lethal phenotype of a Serca2 negative mouse can be avoided by using an inducible recombinase system such that the timing of deletion of the Serca2 gene can be controlled and delayed until after birth. However, the working examples clearly demonstrate the complexity and unpredictability in choosing an inducible system which is capable of producing a homozygous deletion through recombination of inserted recombination sites. The working

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example reports a first attempt to generate an inducible Cre and homozygous floxed Serca2 mouse where the inducible Cre system comprises MLC-2v Cre. The working example teaches that Serca2-flox mice, whose genome comprises a homozygous insertion of loxP sites flanking exons 2 and 3 of the Serca2 gene, were crossed with MLC-2v Cre knock-in mice. However, the specification reports that the inventors were in fact unable to generate the expected Serca2 flox/flox MLC2v wt/Cre mouse. Further analysis revealed that linkage between the *atp2a2* and *myl2* genes on chromosome 5 was 100%, thus preventing generation of the Serca2 flox/flox MLC2v wt/Cre genotype. This example demonstrates that even though the inventors expected to be able to generate the desired genotype, unexpected and unpredictable linkage problems prevented the generation of the desired genotype. However, when the applicant's switched to a different inducible Cre system, where the encoded Cre protein was an inactive Mer-Cre-Mer protein whose activity can be induced by tamoxifen, the applicant's were able to generate Serca2 flox/flox MCM mice. The working example using this mouse further demonstrate knock out of Serca2 following tamoxifen administration to adult mice resulting in the development of heart failure by day 52. However, for the reasons discussed above and below, this single example of specific mouse genotype which generates a heart failure phenotype useful as a disease model, does not provide enablement for the scope of the instant claims as written.

At the time of filing, the prior art did not consider the phenotype of a knock-out or transgenic mouse to be predictable. In addition, the art did not consider the correlation between any observed mouse phenotypes and human disease phenotypes as predictable. Doetschmann et al. teaches that "[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or

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they don't seem to have any phenotype" (Doetschmann (1999) Lab. Animal Sci., Vol. 49 (2), 137-143, see page 137, column 1, paragraph 1). Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice. Moens et al. further teaches that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (Moens et al. (1993) Development, Vol. 199, 485-499). Further, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al. (1992) Nature, Vol. 359, 295-300). Likewise, whereas HPRT deficiency in humans is associated with Lesch-Nyhan syndrome, a severe neurological disorder, HPRT-deficient mice are phenotypically normal (Kuehn et al. (1987) Nature, Vol. 326, 295-298 and Jaenisch (1988) Science, Vol. 240, 1468-1474). Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans. It is further noted that specification itself demonstrates the unpredictability in regards to the particular constructs used in the specification to produce a "null" disruption.

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Therefore, it is maintained that in view of the art recognized unpredictability in determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans, the unpredictability in correlating any observed phenotype in a knockout mouse with gene disruption as acknowledged by the prior art, the art recognized problems with early lethality in Serca ATPase knockout mice, the unpredictability in using any inducible recombinase system to generate a homozygous floxed Serca ATPase/ Cre mouse as evidenced by the working examples, the breadth of potential mutations encompassed by the insertion of two or more recombination sites into any location in a Serca ATPase gene, and the general breadth of the claims as written, it would have required undue experimentation to make and use the scope of the instant invention as claimed.

The rejection of claim 56 under 35 U.S.C. 112, second paragraph, for indefiniteness is maintained. Applicant's amendment to the claims and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that claim 55 as amended defines that both copies of a Serca ATPase genes is modified, and that claim 56 as amended clarifies that more than one Serca ATPase gene is modified. In response, claim 56 as amended continues to be indefinite due to its use of the phrase "several copies of the modified Serca ATPase gene". As previously noted, mice have only two copies of each gene in their genome. While it is understood that there is more than one Serca ATPase gene, Serca1, Serca2, Serca3, each of these genes has only two gene copies.

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Claim 56 continues to indicate that "several" copies of the modified gene are present the mouse. The term "several" encompasses more than two copies of the gene. Thus, the metes and bounds of the claim cannot be determined and claim 56 is indefinite. It is suggested that applicant amend claim 56 to recite, "[t]he mouse of claim 55 comprising more than one modified Serca ATPase gene.....".

Claim Rejections - 35 USC § 103

The rejection of claims 55-57, and 59-68 under 35 U.S.C. 103(a) as being unpatentable over Periasamy et al. (1999) J. Biol. Chem., Vol. 274(4), 2556-2562, in view of Sohal et al. (2001) Circ. Res., Vol. 89, 20-25 is maintained and further applied to new claims 110-116. Applicant's amendment, arguments, and supporting evidence in the form of several publications have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that the skilled artisan would not have been motivated to try and make an adult SERCA2 inducible homozygous knock-out mouse because the prior art teaches that SERCA2 was critical for heart function in adults such that homozygous knockout of the SERCA2 gene would have been expected to be instantly lethal in the adult mouse. The applicant cites several publications in support of this argument for SERCA2 function in adult hearts, including Ver Heyen et al., Bers et al., Periasamy et al. (2001), and Shull et al. The applicant therefore argues that the specification demonstrates "unexpected results" by showing that tamoxifen administration to transgenic mouse in which both endogenous genomic copies of the

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SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α -MHC promoter survive for 52 days before succumbing to heart failure.

In response, it is first noted that only claims 110-111 actually recite that the SERCA2 gene is disrupted. Further, none of the claims place any limitation on the length of survival of the mouse once the SERCA2 gene is homozygously disrupted through recombination. It is also noted that the importance of SERCA2 to cardiac function as taught by Ver Heyen et al., Bers et al., Periasamy et al. (2001), and Shull et al. is not disputed. However, none of these cited references teach or suggest that loss of SERCA2 activity in an adult mouse heart would be instantly lethal as argued by applicants. The closest prior art concerning the effects of loss of SERCA2 function in adult heart continues to be provided by Periasamy et al., as cited in the instant rejection, who shows that an approximately 35% reduction in SERCA2 activity corresponding to loss of one gene in the heterozygous knockout mouse, while affecting cardiac function, does not lead to heart disease. Periasamy et al., as set forth in the rejection of record, was also cited for providing motivation for determining the effects of a complete loss of SERCA2 on adult cardiac function. While Periasamy et al. found that lack of SERCA2 function during embryonic development is lethal, the motivation provided by Periasamy et al. to investigate the loss of function of the SERCA2 gene in adult heart would have led the skilled artisan to combine the teachings of Periasamy et al. with those of Sohal et al., whose inducible and cardiac tissue specific tamoxifen Cre-Lox system can be used generate disruptions in genes known to embryonic lethal, such that the effects of the loss of SERCA2 on cardiac function in the adult could be observed.

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Finally, in regards to the argument for “unexpected results”, it is noted that the any evidence of “unexpected results” must be commensurate in scope with the claimed invention. MPEP 716.02. The specification discloses a single transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α -MHC promoter, wherein the administration of tamoxifen result in the Cre mediated deletion of exons 2 and 3 in both copies of the SERCA2 gene, and wherein the mouse develops heart failure by day 52 following tamoxifen administration. There is no evidence of record for any other embodiment of the claimed invention which demonstrates the alleged “unexpected” survival for more than 50 days. Further, as discussed above, the submitted evidence in the form of publications from the prior art does not support applicant’s argument that the skilled artisan would have expected an adult mouse with an induced null mutation in both copies of the SERCA2 gene to die instantly.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197.

Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633

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